

## Complete Summary

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### GUIDELINE TITLE

The role of aromatase inhibitors in adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: a clinical practice.

### BIBLIOGRAPHIC SOURCE(S)

Eisen A, Trudeau M, Sinclair S, Breast Cancer Disease Site Group. The role of aromatase inhibitors in adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Oct 25. Various p. (Evidence-based series; no. 1-18). [42 references]

### GUIDELINE STATUS

This is the current release of the guideline.

The Evidence-based Series report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

## COMPLETE SUMMARY CONTENT

SCOPE  
METHODOLOGY - including Rating Scheme and Cost Analysis  
RECOMMENDATIONS  
EVIDENCE SUPPORTING THE RECOMMENDATIONS  
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS  
CONTRAINDICATIONS  
QUALIFYING STATEMENTS  
IMPLEMENTATION OF THE GUIDELINE  
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT  
CATEGORIES  
IDENTIFYING INFORMATION AND AVAILABILITY  
DISCLAIMER

## SCOPE

### DISEASE/CONDITION(S)

Early-stage, hormone receptor-positive breast cancer

## GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

## CLINICAL SPECIALTY

Oncology

## INTENDED USERS

Physicians

## GUIDELINE OBJECTIVE(S)

In postmenopausal women with early-stage, hormone receptor-positive breast cancer:

- To evaluate if adjuvant aromatase inhibitors (anastrozole, letrozole, or exemestane) alone for five years compared with adjuvant tamoxifen alone for five years, improve clinically meaningful outcomes (disease-free or overall survival)
- To evaluate if adjuvant aromatase inhibitors in sequence with tamoxifen for a total of five years compared with adjuvant tamoxifen alone for five years, improve clinically meaningful outcomes
- To evaluate if aromatase inhibitors after five years of adjuvant tamoxifen therapy compared with placebo, improve clinically meaningful outcomes
- To evaluate the harms associated with aromatase inhibitors compared with tamoxifen or placebo
- To evaluate if the efficacy of aromatase inhibitors depend on p185 human epidermal growth factor receptor 2 <sup>(HER2)/neu</sup> glycoprotein expression, compared with tamoxifen

## TARGET POPULATION

Postmenopausal women with early-stage, hormone receptor-positive breast cancer

## INTERVENTIONS AND PRACTICES CONSIDERED

1. Adjuvant tamoxifen alone
2. Adjuvant aromatase inhibitors (anastrozole, letrozole, or exemestane) alone and in sequence with tamoxifen
3. Monitor adverse effects of aromatase inhibitors

## MAJOR OUTCOMES CONSIDERED

- Disease-free survival
- Overall survival
- Adverse events
- Menopausal symptoms

- Quality of life

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)  
 Hand-searches of Published Literature (Secondary Sources)  
 Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

#### Literature Search Strategy

MEDLINE was searched to January 2005 using a disease-specific medical subject heading (MeSH) descriptor ("breast neoplasms"), a treatment-specific MeSH descriptor ("chemotherapy, adjuvant"), and an agent-specific MeSH descriptor with qualifier ("aromatase/antagonists and inhibitors"). The Excerpta Medica database (EMBASE) was also searched up to January 2005 using a disease-specific Excerpta Medica Tree (EMTREE) term ("breast cancer"), a treatment-specific keyword ("adjuvant chemotherapy"), and agent-specific EMTREE terms ("anastrozole" or "letrozole" or "exemestane"). These terms were then combined with the search terms for the following publication types: practice guideline, randomized controlled trial, systematic review, or meta-analysis.

Issue 3 (2004) of the Cochrane Library and online conference proceedings from the American Society of Clinical Oncology (ASCO) (<http://www.asco.org/ac/1,1003,12-002095,00.asp>; 1999-2004) and the San Antonio Breast Cancer Symposium (<http://www.sabcs.org/SymposiumOnline/index.asp#abstracts>; 2001-2003) were also searched. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guideline Clearinghouse (<http://www.guideline.gov/>) were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

#### Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- Third-generation aromatase inhibitors as adjuvant hormone therapy in postmenopausal patients with early-stage breast cancer were evaluated using any of the publication types listed in the search strategy (practice guideline, randomized controlled trial, systematic review, or meta-analysis).
- Reported outcomes included disease-free survival (DFS), overall survival, quality of life, or adverse effects of treatment.
- Clinical trial results were reported in full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that

from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and add to the evidence available from fully published studies. Those data often appear first in meeting abstracts and may not be published for several years.

#### Exclusion Criteria

Trials published in a language other than English were excluded.

#### NUMBER OF SOURCE DOCUMENTS

Seven randomized controlled trials, described in 20 reports, and one practice guideline, described in two reports, were eligible for inclusion in the systematic review of the evidence.

#### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

#### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

#### METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

#### DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Due to the preliminary and varied nature of the evidence, the aromatase inhibitor data for early-stage breast cancer was not pooled.

#### METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

#### DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

For a complete discussion of the methods used to formulate the recommendations, please refer to the "Discussion" section of the original guideline document.

#### RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

#### COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

## METHOD OF GUIDELINE VALIDATION

External Peer Review  
Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 127 practitioners in Ontario (74 medical oncologists, 33 radiation oncologists, and 20 surgeons). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on October 4, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer Disease Site Group (DSG) reviewed the results of the survey.

The final Evidence-based Series report was reviewed and approved by one member of the Program in Evidence-based Care (PEBC) Report Approval Panel with expertise in clinical and methodology issues.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

Question 1 -- Compared with Adjuvant Tamoxifen Alone for Five Years, Do Adjuvant Aromatase Inhibitors (Anastrozole, Letrozole, or Exemestane) Alone for Five Years Improve Clinically Meaningful Outcomes (Disease-Free or Overall Survival)?

- Adjuvant tamoxifen (20mg daily for five years) remains a recommended standard of care for women with hormone receptor-positive breast cancer.
- Adjuvant anastrozole (1mg daily for five years) is also a recommended standard of care for women with hormone receptor-positive breast cancer. Additionally, anastrozole is the preferred hormone treatment for postmenopausal women with hormone receptor-positive breast cancer who are thought to have a relative or absolute contraindication to tamoxifen or who have significant adverse effects with tamoxifen therapy.

Question 2 -- Compared with Adjuvant Tamoxifen Alone for Five Years, Do Adjuvant Aromatase Inhibitors in Sequence with Tamoxifen for a Total of Five Years Improve Clinically Meaningful Outcomes?

- Adjuvant tamoxifen (20mg daily for five years) remains a recommended standard of care for women with hormone receptor-positive breast cancer.
- Adjuvant exemestane therapy (25mg daily, to a total of five years of hormone therapy) is also a recommended standard of care for postmenopausal women

with hormone receptor-positive breast cancer who have completed two to three years of tamoxifen treatment.

Question 3 -- Compared with Placebo, Do Aromatase Inhibitors after Five Years of Adjuvant Tamoxifen Therapy Improve Clinically Meaningful Outcomes?

- Postmenopausal women with hormone receptor-positive tumours who have completed five years of adjuvant tamoxifen therapy (20mg daily) should be considered for letrozole treatment (2.5mg daily for five years).

Question 4 -- Compared with Tamoxifen or Placebo, What Are the Harms Associated with Aromatase Inhibitors?

- Women receiving aromatase inhibitors should be monitored for changes in bone mineral density.

Question 5 -- Compared with Tamoxifen, Does the Efficacy of Aromatase Inhibitors Depend on p185<sup>HER2</sup>/neu Glycoprotein Expression?

- Due to the lack of evidence, no recommendation for the use of aromatase inhibitors based on human epidermal growth factor receptor 2 (HER2)/neu status could be made.

#### CLINICAL ALGORITHM(S)

None provided

### EVIDENCE SUPPORTING THE RECOMMENDATIONS

#### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and one practice guideline.

### BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

#### POTENTIAL BENEFITS

Question 1 -- Compared with Adjuvant Tamoxifen Alone for Five Years, Do Adjuvant Aromatase Inhibitors (Anastrozole, Letrozole, or Exemestane) Alone for Five Years Improve Clinically Meaningful Outcomes (Disease-Free or Overall Survival)?

The Arimidex (anastrozole) or Tamoxifen Alone or in Combination study (n=9,366) compared tamoxifen versus anastrozole versus tamoxifen plus anastrozole. At 68 months (5.7 years), disease recurrence was improved in the anastrozole group versus the tamoxifen group (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.78 to 0.97; p=0.03). The absolute difference in the

four-year, disease-free survival estimates was 2.4% (86.9% with anastrozole versus 84.5% with tamoxifen). Overall survival was not significantly different.

Question 2 -- Compared with Adjuvant Tamoxifen Alone for Five Years, Do Adjuvant Aromatase Inhibitors in Sequence with Tamoxifen for a Total of Five Years Improve Clinically Meaningful Outcomes?

The Intergroup Exemestane Study (n=4,742) compared two to three years of tamoxifen followed by exemestane with two to three years of tamoxifen followed by further tamoxifen, each to a total of five years of adjuvant hormone therapy. Three-year, disease-free survival estimates at 30.6 months median follow-up were 91.5% (95% CI, 90.0% to 92.7%) in the exemestane group and 86.8% (95% CI, 85.1% to 88.3%) in the tamoxifen group (4.7% absolute difference). At 37.4 months, recurrence rates favoured exemestane after tamoxifen (HR, 0.73; 95% CI, 0.62 to 0.86; p=0.0001). Overall survival was not different at the time of this analysis (HR, 0.83; 95% CI, 0.67 to 1.02; p=0.08).

Question 3 -- Compared with Placebo, Do Aromatase Inhibitors after Five Years of Adjuvant Tamoxifen Therapy Improve Clinically Meaningful Outcomes?

The MA-17 study (n=5,187) compared letrozole to placebo following 4.5 to six years of tamoxifen. In an interim analysis at 2.4 years, there was an improvement in disease-free survival favouring letrozole over placebo (HR, 0.57; 95% CI, 0.43 to 0.75; p=0.00008). The estimated four-year, disease-free survival rates were 93% with letrozole versus 87% with placebo (6% absolute difference). The final analysis at 2.5 years continues to show improved rates of recurrence (42% reduction in risk, p=0.0004). In the whole sample, overall survival was not significantly different at either analysis. In the final analysis, overall survival was significantly improved with letrozole in node-positive women (HR, 0.61; 95% CI, 0.38 to 0.98; p=0.04) but not in node-negative women (HR, 1.52; 95% CI, 0.76 to 3.06; p=0.24).

Question 4 -- Compared with Tamoxifen or Placebo, What Are the Harms Associated with Aromatase Inhibitors?

Compared with tamoxifen, preliminary evidence exists to suggest that aromatase inhibitors reduce the occurrence of venous thromboembolic and gynecologic events.

#### POTENTIAL HARMS

- Compared with tamoxifen or placebo, aromatase inhibitors likely increase the occurrence of bone events, including fractures and osteoporosis. Early data on clinical cardiac outcomes and lipid profile changes are mixed.
- Compared with placebo, letrozole may adversely affect quality of life and increase the occurrence of arthritis and/or arthralgia.

#### CONTRAINDICATIONS

#### CONTRAINDICATIONS

Aromatase inhibitors are contraindicated for premenopausal women.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

Question 1 -- Compared with Adjuvant Tamoxifen Alone for Five Years, Do Adjuvant Aromatase Inhibitors (Anastrozole, Letrozole, or Exemestane) Alone for Five Years Improve Clinically Meaningful Outcomes (Disease-Free or Overall Survival)?

- Tamoxifen remains a recommended standard of care for two reasons. First, to date there has been no overall survival benefit detected for anastrozole over tamoxifen. Second, the evidence indicates that patients treated with aromatase inhibitors experience greater loss of bone mineral density. Third, based on the excess incidence of myocardial infarction in the Intergroup Exemestane Study (IES) trial, and the non-statistically significant two-fold increase in cardiac deaths in the Breast International Group (BIG) 1-98 trial, it is the expert opinion of the Breast Cancer Disease Site Group (DSG) that concerns regarding cardiac toxicity with aromatase inhibitors are justified. Therefore, especially for women at a low risk of recurrence or high risk of known complications, or both, tamoxifen may still be the preferred therapy option.
- Letrozole may be an alternative to anastrozole. The Breast International Group 1-98 trial compared letrozole versus tamoxifen in 8,028 women. After a median follow-up of 35.5 months, patients treated with letrozole had significantly better disease-free survival versus those treated with tamoxifen (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.70 to 0.93). However, that trial has to date only been published in abstract form, and the results have not been widely disseminated. No specific recommendation can be made until the final results are published.

Question 2 -- Compared with Adjuvant Tamoxifen Alone for Five Years, Do Adjuvant Aromatase Inhibitors in Sequence with Tamoxifen for a Total of Five Years Improve Clinically Meaningful Outcomes?

- Tamoxifen remains a recommended standard of care for the reasons described in the qualifying statement for Question 1.
- Although more definitive results from larger trials are required, early results from the Italian Tamoxifen Arimidex trial suggest that, for women who need to discontinue tamoxifen after two to three years, anastrozole may be a reasonable alternative to exemestane. The Italian Tamoxifen Arimidex (anastrozole) trial (n=426) compared tamoxifen (20mg daily) for two or more years followed by further tamoxifen or anastrozole (1mg daily) to a total of five years of adjuvant hormone therapy. At 24 months (two years), recurrence was improved in women who switched to anastrozole (hazard ratio, 0.36; 95% confidence interval, 0.17 to 0.75; p=0.006). The absolute difference in the percentage of women who experienced a recurrence was 5.4% (9.1% with tamoxifen and 3.7% with anastrozole). Overall survival was not significantly different at the time of the analysis (hazard ratio, 0.18; 95% confidence interval, 0.02 to 1.57; p=0.07).

- Women in the Intergroup Exemestane Study and the Italian Tamoxifen Arimidex (anastrozole) trial received tamoxifen for at least two years. Decisions regarding initiating aromatase inhibitors in those who have taken tamoxifen for less than two years will have to be individualized.

Question 3 -- Compared with Placebo, Do Aromatase Inhibitors after Five Years of Adjuvant Tamoxifen Therapy Improve Clinically Meaningful Outcomes?

- To date, there are only data for the first 2.5 years of letrozole treatment after five years of adjuvant tamoxifen therapy. Clinicians and patients should expect to review the question of letrozole treatment duration as more data on efficacy and toxicity become available over the next several years.
- Patients in the MA-17 trial were treated within three months of stopping tamoxifen and had received tamoxifen for 4.5 to 6 years. Decisions regarding the initiation of letrozole therapy in women who have been off tamoxifen for more than three months will have to be individualized, based on the time since tamoxifen was discontinued, the prognosis of the patient, and the toxicity of treatment. Similarly, decisions regarding the initiation of letrozole in those who have taken tamoxifen for three to 4.5 years will have to be individualized.

Question 4 -- Compared with Tamoxifen or Placebo, What Are the Harms Associated with Aromatase Inhibitors?

- Due to theoretical concerns and the lack of long-term data, clinical cardiac outcomes and lipid profile changes, as well as other harms associated with aromatase inhibitors, should be monitored.
- Aromatase inhibitors are contraindicated for premenopausal women.

Question 5 -- Compared with Tamoxifen, Does the Efficacy of Aromatase Inhibitors Depend on p185HER2/neu Glycoprotein Expression?

- Based on the neoadjuvant trial evidence, it is the opinion of the Breast Cancer Disease Site Group that aromatase inhibitors may be the preferred treatment in women with human epidermal growth factor receptor 2 (HER2)/neu-overexpressing breast cancer.

#### General Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Eisen A, Trudeau M, Sinclair S, Breast Cancer Disease Site Group. The role of aromatase inhibitors in adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Oct 25. Various p. (Evidence-based series; no. 1-18). [42 references]

### ADAPTATION

Not applicable: The guideline was not adapted from another source.

### DATE RELEASED

2005 Oct 25

### GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

### GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

### SOURCE(S) OF FUNDING

Cancer Care Ontario  
Ontario Ministry of Health and Long-Term Care

### GUIDELINE COMMITTEE

Provincial Breast Cancer Disease Site Group

## COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

## FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Breast Cancer Disease Site Group (DSG) disclosed potential conflicts of interest relating to the topic of this practice guideline. Two of the lead authors (AE, MT) reported related research involvement. These authors reported receiving honoraria or consultant fees from pharmaceutical companies that manufacture the aromatase inhibitors covered by this review.

## GUIDELINE STATUS

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Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

## GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

## AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of aromatase inhibitors in adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer. Evidence-based series. Toronto (ON): Cancer Care Ontario (CCO), 2005 Oct 25. Various p. (Practice guideline; no. 1-18: Section 1). Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995; 13(2):502-12.

## PATIENT RESOURCES

None available

## NGC STATUS

This summary was completed by ECRI on January 24, 2006. The information was verified by the guideline developer on February 23, 2006.

## COPYRIGHT STATEMENT

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